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Systematic review and a proposal for clinical practice

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Allocation of patients with liver cirrhosis and organ failure to intensive care: Systematic review and a proposal for clinical practice

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Abstract

AIM: To propose an allocation system of patients with liver cirrhosis to intensive care unit (ICU), and developed a decision tool for clinical practice.

METHODS: A systematic review of the literature was performed in PubMed, MEDLINE and EMBASE databases. The search includes studies on hospitalized patients with cirrhosis and organ failure, or acute on chronic liver failure and/or intensive care therapy.

RESULTS: The initial search identified 660 potentially relevant articles. Ultimately, five articles were selected; two cohort studies and three reviews were found eligible. The literature on this topic is scarce and no studies specifically address allocation of patients with liver cirrhosis to ICU. Throughout the literature, there is consensus that selection criteria for ICU admission should be developed and validated for this group of patients and multidisciplinary approach is mandatory. Based on current available data we developed an algorithm, to determine if a patient is candidate to intensive care if needed, based on three scoring systems: pre-morbid Child-Pugh Score, Model of End stage Liver Disease score and the liver specific Sequential Organ Failure Assessment score.

CONCLUSION: There are no established systems for allocation of patients with liver cirrhosis to the ICU and no evidence-based recommendations can be made.

Key words: Cirrhosis; Failure; Intensive care; Allocation; Treatment

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Core tip: The literature regarding allocation of cirrhotic patients to intensive care unit (ICU) is very limited and no studies have proposed and tested any specific allocation criteria. Thus it still remains to be determined, which cirrhotic patients will benefit from intensive care treatment, and if so, when during admission they should be transferred to the ICU, and when intensive treatment is futile and should be withheld. We propose an allocation system for clinical practice, based on internationally validated scoring systems.

Lindvig KP, Teisner AS, Kjeldsen J, Strøm T, Toft P, Furrhmann V, Krag A. Allocation of patients with liver cirrhosis and organ failure to intensive care: Systematic review and a proposal for clinical practice. *World J Gastroenterol* 2015; 21(29): 8964-8973 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i29/8964.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i29.8964>

INTRODUCTION

The incidence of liver cirrhosis is increasing^[1,2]. In the western world liver cirrhosis is mainly related to the increasing burden of alcohol-related liver disease, non-alcoholic fatty liver disease and currently also hepatitis C, in the eastern world hepatitis B is a main cause. Patients with liver cirrhosis are prone to a progressive deterioration with the occurrence of portal hypertension and hepatic failure leading to end-stage liver disease and the development of complications. Furthermore, a large group (up to 75%) of patients are first diagnosed with liver cirrhosis, when experiencing their first episode of decompensation, and thus these patients represents a large hidden burden of the disease^[3]. Patients with advanced liver cirrhosis, frequently require admission to intensive care unit (ICU)^[4], mainly for various complications of advanced liver disease (*i.e.*, sepsis, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato-renal syndrome). These complications are associated with high risk of organ failures and a high mortality. Patients with cirrhosis presenting with acute hepatic deterioration and progressive organ failure represent the, now well described, syndrome acute-on-chronic-liver failure (ACLF)^[5,6]. The Chronic Liver Failure (CLIF) ACLF in cirrhosis (CANONIC) study investigators of the European Association for the Study of the Liver - Chronic Liver Failure Consortium (EASL-CLIF) originally introduced the concept of ACLF: "ACLF is based on the presence of three major characteristics of the syndrome; acute decompensation, organ failure [predefined by the Clif Sequential Organ Failure Assessment (SOFA) score]

and high 28-d mortality rate^[6]". Since ACLF affects approximately 30% of hospitalised cirrhotic patients, ACLF is the most frequent indication for admission to the ICU^[4,5]. However, the mortality among patients admitted to the ICU with ACLF is high^[7]. Consequently, clinical awareness on identification of cirrhotic patients at risk of developing organ failure, who will benefit from early intensive care treatment, is of great importance. The mortality among patients admitted to the ICU with ACLF ranges between 35%-93%^[2,5,7]. Patients requiring mechanical ventilation are high-risk patients with poor long-term survival with a 1-year mortality rate of 89%^[8]. Kavli *et al*^[7] have shown that among patients with clinical or histological diagnosed alcoholic liver cirrhosis, in need for intensive care treatment, the 90-d mortality reaches levels of up to 93%, dependent on the degree of organ system failure^[7]. Due to the poor prognosis the utilization of organ support in the ICU for these patients is often questioned. The treatment of patients with ACLF, not eligible for liver transplantation, is complicated and must be managed with therapies, which require a highly specialized team and close collaboration between hepatologists and intensive care specialists. There is a need for clinical tools and a proper triage to guide the physicians in decision making regarding the allocation of patients with ACLF to ICU, admitting only patients who would likely benefit from intensive care treatment^[7]. In this study we aimed to perform a systematic review regarding allocation of patients with liver cirrhosis to intensive care, and to propose a decision tool for clinical practice.

MATERIALS AND METHODS

An electronic search was performed in PubMed, MEDLINE and EMBASE. Studies were included in the search irrespective of blinding, publication status, or language, and manual searches including scanning of reference lists in relevant articles and conference proceedings was also performed. All studies responding to the issue of this article were eligible for analysis, including previous reviews.

Criteria for considering studies for this review

The present systematic search includes studies on hospitalized patients with cirrhosis and organ failure or acute on CLIF and/or intensive care therapy.

Search methods for identification of studies

String 1: "liver cirrhosis" or "hepatic cirrhosis"; String 2: "liver failure" or "hepatic failure"; String 3: "intensive care" or "intensive treatment" or "intensive therapy" or "critical care".

Potentially eligible studies were listed and evaluated. After reading the titles and abstracts, clearly irrelevant trials were excluded. Afterwards relevant full text studies were evaluated, and the eligible studies

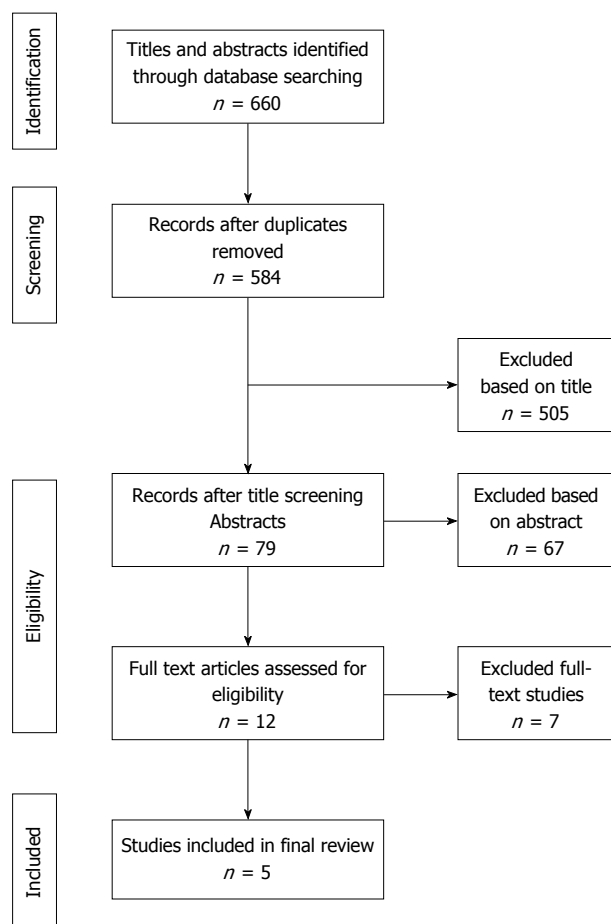


Figure 1 Flowchart of trials. Flowchart of search string.

were selected (Figure 1).

RESULTS

The initial search identified 660 articles, 402 articles were indexed in PubMed, and 258 indexed in EMBASE. After duplicates were removed 584 articles, were evaluated for relevance.

During the initial title screening process 505 articles were evaluated by title of the first author, and found not relevant for the specific topic of this article, and thereby excluded from the study. Further 67 articles were excluded after reading the abstracts, leaving 12 potentially relevant articles to be evaluated in full text together with a review of references in these articles. Ultimately, five articles were selected; two cohort studies and three reviews were found in the systematic search to be eligible for the present review (Figure 1). Table 1 summarizes the main findings of the included studies.

Cohort studies

Kavli *et al.*^[7] performed a retrospective cohort study including 87 patients admitted to an ICU, at a university hospital with primary and secondary referrals. They found that increasing numbers of organ failures, correlate with increased mortality in critically ill patients

with alcoholic liver cirrhosis. Interestingly they found that in patients with 3 or more organ failures the ICU mortality was > 90% (Table 1). Furthermore, they found the prognostic scores specific for critical illness to be superior at predicting outcome compared to the liver-specific Child-Pugh score.

Shawcross *et al.*^[1] performed a prospective analysis of 563 patients admitted to a liver ICU with diagnosis of cirrhosis and dysfunction of one or more extrahepatic organ(s). They assessed resource utilization and found that presence of organ failure resulted in considerable resource expenditure in patients with liver cirrhosis, but had hospital mortality of 59% as illustrated in Table 1.

Reviews

Ginès *et al.*^[9] performed a review with focus on the diagnostic approach and the currently recommended treatment strategy of critically ill cirrhotic patients. They report no new data, and no methods section is described. However, they describe that several studies have shown that relatively good results can be obtained in selected critically ill cirrhotic patients, and therefore reluctance to refer these patients to the ICU should be balanced. They suggest that patients with a low Model of End-stage Liver Disease (MELD score) (< 15) should be immediately considered for ICU. Contrary, in patients with end-stage cirrhosis (MELD > 30), 3 or more organ failures, and no perspective of transplantation, aggressive management is questionable.

Berry *et al.*^[10] performed a review within the field of cirrhotic patients and allocation to ICU. They reported no new data, and the methods section was sparsely described. They suggest that an aggressive approach to organ support is justified, and that further discussions between hepatologists and intensive care specialists are required to determine acceptable burden-to-benefit ratios for prolonged intensive care support in young alcoholic patients.

Saliba *et al.*^[11] performed a review within the field of cirrhotic patients and allocation to ICU. They reported no new data, and no methods section was described. However, they claimed that general ICU prognostic scores [SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) II and SAPS II] predicted mortality better than liver specific scores (MELD and Child-Pugh score) in cirrhotic patients, once admitted to the ICU. Furthermore, ICU and liver scores predicted outcome more precisely once they were re-evaluated at day 3 from admission. The authors stated that patients should be referred from the hepatology ward to the ICU at an earlier stage of decompensation, and a multidisciplinary approach between hepatologists, intensive care specialists, and also transplant surgeons should be mandatory.

Scoring systems

A number of score systems have been developed to assess the prognosis of critically ill cirrhotic patients,

Table 1 Included trials/studies

Author, year, location, study design	Main target of the study	Patient population	Scores	Allocation system	In hospital mortality	ICU mortality
Kavli <i>et al</i> ^[7] , 2012, Denmark, cohort study	This study investigated the severity of organ failure, and the frequency and outcome of withholding therapy in patients with advanced alcoholic liver cirrhosis admitted to a Scandinavian ICU	87 adult patients with clinical or histological diagnosis of liver cirrhosis admitted to ICU at a University hospital in Denmark, within a 3 years period from January 2007-January 2010	APACHE II, SAPS II, and SOFA were better at predicting mortality than Child-Pugh score	No specific allocation system is proposed	Only ICU data	With 3 or more organ failures the ICU mortality was > 90%
Shawcross <i>et al</i> ^[1] , 2012, United Kingdom, cohort study	The aim of this study was to prospectively study the resource allocation and cost of a large cohort of patients with cirrhosis and one or more extrahepatic organ failure(s)	563 patients were admitted to the Liver ICU at King's College Hospital, between 2000 and 2007	The median (IQR) for all patients admitted and surviving for > 8 h on day 1 (<i>n</i> = 548) was Child-Pugh score 12 (11-13), MELD 25 (14-34), APACHE II 22 (16-28) and SOFA 11 (8-13)	No specific allocation system is proposed Patients with cirrhosis admitted to ICU require high levels of organ support but ICU admission is not necessarily futile	Overall hospital mortality of 59% (330/563)	256/563 (51%) patients died whilst in the Liver ICU
Ginès <i>et al</i> ^[9] , 2012, Spain, review	This review focuses on the diagnostic approach and treatment strategies currently recommended in the critical care management of patients with cirrhosis	None	MELD and Child-Pugh scores have important limitations in the establishment of prognosis in critically ill cirrhotic patients	Encephalopathic cirrhotic patients (grade 3 or 4 hepatic encephalopathy) require ICU admission and intubation Patients with a low MELD score (< 15), should be immediately considered for ICU. Contrary, in patients with end-stage cirrhosis (MELD > 30), 3 or more organ failures, and no perspective of transplantation, aggressive management is questionable No specific allocation system is proposed	Hospital mortality rates in patients with 1, 2 or 3 organ/system failures were 48%, 65%, and 70%, respectively	ICU and 6-mo mortality rates of 41% and 62%, respectively 59% of cirrhotic patients placed on mechanical ventilation died during their stay in the ICU
Berry <i>et al</i> ^[10] , 2013, United Kingdom, review	This review focuses on patients with cirrhosis, especially survival analysis and prognostic models		Child-Pugh score does not perform as well as general critical illness scoring systems The MELD score performs better than the Child-Pugh score, yet the SOFA score is superior to both Child-Pugh and MELD score	Early aggressive approach to organ support is justified	Greater than 60%	ICU mortality of up to 65%, rising to 90% with sepsis, if more than 1 d of respiratory support and renal support were required
Saliba <i>et al</i> ^[11] , 2013, France, review	This review focuses on prognostic scores and admission to ICU for critically ill cirrhotic patients	None	Suggests that ICU scores (SOFA, APACHE II, SAPS II) predict the outcome of cirrhotic patients admitted to the ICU better than liver scores (MELD and Child-Pugh)	No specific allocation system is proposed The persistence after ICU admission of three or more organ failures and the need for three or more organ supports, may lead to consider a limitation in life sustaining treatments, as a fatal outcome is almost constant	Only ICU data	Ranges between 34%-69%

Included studies of the present review. The table describes the included studies. ICU: Intensive care unit; SOFA score: Sequential Organ Failure Assessment score; MELD: Model of End-stage Liver Disease.

Table 2 Scoring systems to predict mortality

Score	Target	Number of studies	AUCROC range (min-max)
Child-Pugh	Prognostic ¹	14	0.71-0.87
MELD	Prognostic ¹	8	0.77-0.93
RFH	Prognostic ¹	1	0.79
SOFA	Organ failure ²	11	0.81-0.95
APACHE II	Prognostic in ICU ³	9	0.66-0.83
APACHE III	Prognostic in ICU ³	4	0.78-0.91

¹Prognostic: score used to assess the prognosis of chronic liver disease;

²Organ failure: score with the objective to evaluate the degree of organ failure; ³Prognostic in ICU: severity of disease classification score. The table describes the performance of the presented scoring systems^[17,19-35]. AUROC: Areal Under the Receiver Operating Curve; Range (min-max) describing the minimum and maximum reported AUC for the given score, based on published trials^[17,19-35]. ICU: Intensive care unit; MELD: Model of End-stage Liver Disease; RFH: Royal Free Hospital Score; SOFA: Sequential Organ Failure Assessment score; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 3 Child-Pugh score

Measure	1 point	2 points	3 points
Total bilirubin (μmol/L)	< 34 (< 1.9 mg/dL)	34-50 (1.9-2.9 mg/dL)	> 50 (> 2.9 mg/dL)
S-Albumin (g/L)	> 35	28-35	< 28
PT INR	< 1.70	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate/severe
Hepatic encephalopathy	None	Grade I - II	Grade III-IV
Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Child-Pugh Score and associated one- and two-year survival.

see Table 2^[2,12-35]. The liver specific scores have mainly focused on the general prognosis of cirrhotic patients, whereas the general scores, such as APACHE score, and SOFA score, were developed to predict outcome in the general population admitted to the ICU^[5,14,20]. Numerous organ-failure scores have been developed to evaluate the prognosis depending on the number of organ failures, however, only a limited number of score systems have been established in clinical practice. To assess severity and prognosis due to underlying liver disease before ACLF or acute hospitalization, Child-Pugh score and MELD score are the best-validated scores^[14]. The World Health Organization (WHO) performance status (PS) is also useful to grade general well-being and activities of daily life.

The prognostic liver specific score named Child-Pugh score (Table 3) contains five components; grade of hepatic encephalopathy, presence of ascites, serum-bilirubin, serum-albumin, and the international normalized ratio for prothrombin time (INR)^[36].

Child Pugh score

The Child-Pugh score has been well established in clinical practice for decades. It contains a limited number of variables, is simply calculated, and is easily interpreted. The score is a simple method for determining the prognosis of patients with cirrhosis^[15]. However, the Child-Pugh score does not take factors such as cardiovascular, renal, and pulmonary dysfunction into account, consequently it does not offer valid information to predict mortality in cirrhotic patients who have organ failure^[14]. Further, the assessment of hepatic encephalopathy and presence of ascites are subjective measures and prone to observer variation.

MELD score

The MELD score is a scoring system for assessing the severity of chronic liver disease. The MELD Score ranges from 6 (less sick) to 40 (very sick) and the formula is based on the natural logarithm of serum bilirubin, serum creatinine, the INR for prothrombin time, and information regarding dialysis^[37].

The MELD Score formula: $[0.957 \times \ln[\text{serum creatinine}] + 0.378 \times \ln[\text{serum bilirubin}] + 1.120 \times \ln[\text{INR}] + 0.643] \times 10$ (if hemodialysis, value for Creatinine is automatically set to 4.0).

Serum bilirubin is a blood sample that reflects the liver function. (Reference interval: 5-25 μmol/L). The INR reflects the ability of the liver to produce proteins; more specifically the clotting factors that contribute to the coagulation process (Reference interval: 0.8-1.2 is normal, higher is abnormal). Creatinine is a blood sample that reflects the function of the kidneys. (Reference interval: 60-105 μmol/L).

The MELD score is widely used to quantify end-stage liver disease in patients listed for liver transplantation^[15], and has been repeatedly shown to be equivalent or even superior to the Child-Pugh score to estimate short-term survival among cirrhotic patients^[14]. An additional advantage of MELD is the exclusion of subjective measures.

WHO performance score

The performance score was originally introduced in the treatment of cancer patients, as an attempt to quantify cancer patients' general well-being and activities of daily life (Table 4)^[38]. The score is widely used in other medical conditions as a simple measure of general condition, functional ability and quality of life.

APACHE scores

The APACHE score is one of several ICU scoring systems. The score is a severity-of-disease classification system, based on 12 physiological parameters; 1, alveolar-arterial O₂ tension difference (AaDO₂) or arterial oxygen tension (PaO₂) (depending on the fraction of inspired oxygen); 2, temperature (rectal); 3, mean arterial pressure; 4, arterial pH; 5, heart rate;;

Table 4 World Health Organization performance score

Grade	WHO Performance score
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, <i>e.g.</i> , light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare, totally confined to bed or chair
5	Dead

WHO: World Health Organization.

6, respiratory rate; 7, sodium (serum); 8, potassium (serum); 9, Creatinine; 10,. Haematocrit; 11, white blood cell count; and 12; Glasgow Coma Scale. The score is applied within 24 h of admission to the ICU, the higher the score, the higher risk of death^[15]. Compared to Child-Pugh scores it has been shown in numerous studies to be more powerful in predicting hospital mortality in patients with liver cirrhosis. Wehler *et al.*^[39] found an areal under the receiver operating curve (AUROC) of 0.79 for the APACHE II score, compared to Child-Pugh with an AUROC of 0.73, other studies have found similar results^[24-26,28].

SOFA Score and CLIF-SOFA

The SOFA score was developed as a simple prognostic score to evaluate the degree of organ failure in patients in the general ICU^[2,29]. The score contains information on degree of failure regarding liver, kidney, brain, coagulation, circulation and lungs, graded from 0-4 (Table 5). The CLIF-SOFA score is a modified version of the original SOFA score, a newly developed scoring system exclusively for patients with end-stage liver disease, and it accommodates a lower threshold for serum creatinine, because minor increases in s-creatinine levels in cirrhotic patients indicate marked reductions in glomerular filtration rate. Furthermore, it uses the INR instead of platelets as a marker of coagulaopathy, increases the threshold for bilirubin to achieve organ failure, and uses grades of hepatic encephalopathy from the West Haven score as opposed to Glasgow Coma Scale for neurologic failure^[2,6]. Organ failure in the CLIF SOFA score is defined as; liver failure: bilirubin > 205 $\mu\text{mol/L}$, kidney failure: creatinine > 177 $\mu\text{mol/L}$ or requiring renal replacement therapy, neurologic failure: hepatic encephalopathy grade 3 or 4, coagulation failure: INR > 2.5, and circulation failure: requiring vasopressors to maintain adequate mean arterial pressure (MAP). The CLIF-SOFA score can be translated into a degree of ACLF^[6,40] (Figure 2, Tables 5 and 6).

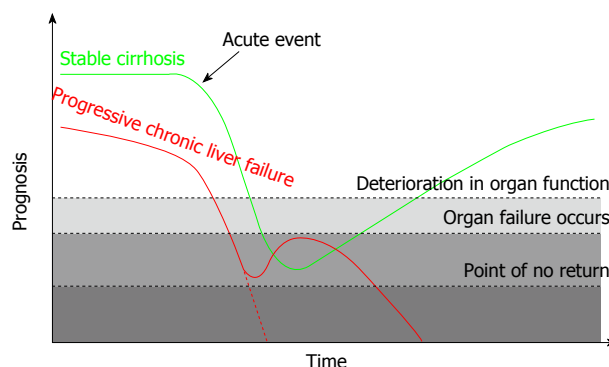


Figure 2 Acute on Chronic Liver Failure. The green line illustrates a patient with stable cirrhosis (*i.e.*, Child-Pugh class A/B) developing acute on chronic liver failure (ACLF). The red line illustrates a patient with progressive chronic liver failure (*i.e.*, a patients with Child C cirrhosis and refractory ascites) developing ACLF. The Y-axis (Prognosis) is based on Child Pugh score or MELD score and the performance status before ACLF develops and CLIF-SOFA score after ACLF. The threshold "deterioration in organ function" represents a level with *i.e.* increase in creatinine or oxygen demand without organ failure. The threshold "organ failure" is as defined in the CLIF-SOFA score and "point of no return" is a state of multiorgan failure without reversibility.

Royal Free Hospital score

The Royal Free Hospital (RFH) score is a novel prognostic model for critically ill patients with cirrhosis. Parameters included in the score are bilirubin, INR, lactate, urea, A-a gradient, and variceal bleeding. Theocharidou *et al.*^[18] found the RFH score to have good discriminative power, equally to the CLIF-SOFA and SOFA score, however, the score remains to be externally validated, to confirm the clinical utility.

DISCUSSION

The decision-making regarding allocation of cirrhotic patients to ICU remains a great interdisciplinary challenge in daily clinical practice. The literature is scarce and no studies specifically address this issue. There is general consensus that selection criteria for ICU admission candidates should be developed and validated for this group of patients and multidisciplinary approach is mandatory. However, all together the general approach throughout the literature is somewhat indefinable. It still remains to be determined, which cirrhotic patients will benefit from intensive care treatment, and if so, when during admission they should be transferred to the ICU, and contrary when intensive treatment is futile and should be withheld.

It has been known for more than 40 years that surgical procedures on cirrhotic patients is associated with increased risk^[35], and for cirrhotic patients (child-pugh C) who undergo nontransplant surgical procedures, mortality rates of up to 76% have been reported^[41]. Furthermore it is known that the mortality rate is markedly increased for emergency surgery (57%) compared to elective surgery (10%)^[42]. Higher

Table 5 Chronic Liver Failure-Sequential Organ Failure Assessment score

Organ	Variable	0	1	2	3	4
Liver	Billirubin, $\mu\text{mol/L}$ (mg/dL)	< 20 $\mu\text{mol/L}$ (-1.1)	≥ 20 to < 34 $\mu\text{mol/L}$ (≥ 1.1 to < 1.9)	≥ 34 to < 103 $\mu\text{mol/L}$ (≥ 1.9 to < 6.0)	≥ 103 to < 205 $\mu\text{mol/L}$ (≥ 6.0 to < 11.9)	> 205 $\mu\text{mol/L}$ (> 11.9) ¹
Kidney	Creatinine, $\mu\text{mol/L}$ (mg/dL)	< 106 $\mu\text{mol/L}$ (< 1.2)	≥ 106 to < 177 $\mu\text{mol/L}$ (≥ 1.2 to < 2.0)	≥ 177 to < 309 $\mu\text{mol/L}$ (≥ 1.2 to < 3.5) ¹	≥ 309 to < 442 $\mu\text{mol/L}$ (≥ 3.5 to < 5) ¹	> 442 $\mu\text{mol/L}$ (> 5.0) ¹
CNS	HE grade	None	I	II	III ¹	IV ¹
Coagulation	INR	< 1.1	≥ 1.1 to 1.25	≥ 1.25 to < 1.5	≥ 1.5 to < 2.5	≥ 2.5 or platelets < 20 ¹
Circulation	MAP (mmHg)	≥ 70	< 70	Dopamine ≤ 5 ¹	Dopamine > 5 ¹	Dopamine > 15
				Dobutamine	Epinephrine ≤ 0.1 ¹	Epinephrine > 0.1
				Terlipressin ¹	Norepinephrine ≤ 0.1 ¹	Norepinephrine > 0.1 ¹
Lungs	PaO ₂ /FiO ₂	> 400	> 300 to ≤ 400	> 200 to ≤ 300	> 100 to ≤ 200 ¹	≤ 100 ¹
	SpO ₂ /FiO ₂	> 512	> 357 to ≤ 512	> 214 to < 357	> 89 to ≤ 214 ¹	≤ 89 ¹

¹Indicates the limit for the definition of organ failure. HE: Hepatic encephalopathy; MAP: Mean arterial pressure; PaO₂: Arterial oxygen tension; FiO₂: Fraction of inspired oxygen; SpO₂: Peripheral capillary oxygen saturation.

Table 6 Degree of Acute on Chronic Liver Failure and the associated mortality

ACLF	Numbers of organ failure	28-d mortality	90-d mortality
0	0 or 1 (/kidney)	4.7%	15.0%
1	1 (no kidney dysfunction)	22.1%	40.7%
2	2	32.0%	52.3%
3	≥ 3	76.7%	79.1%

ACLF: Acute on Chronic Liver Failure.

risk of infection, coagulopathy and malnutrition may be important factors^[43-47]. In addition many cirrhotic patients decompensate in the postoperative phase and develop hepatic encephalopathy, ascites, hepato-renal syndrome or infections^[44,45,47,48]. Reduced perfusion of the liver and altered response to anaesthetics and other medications, may also be contributing factors^[49,50]. It is therefore essential to assess the severity of the underlying liver disease and to perform preoperative optimisation, including treatment of coagulopathy, ascites, portal hypertension, malnutrition, any substance abuse problem and infections.

Based on current available data^[5,6], we have developed an algorithm based on three scoring systems: Child-Pugh Score, MELD score and CLIF-SOFA score. In Figure 3 we suggest criteria to determine if a patient is a candidate to intensive care if needed. However, the algorithm remains to be validated in clinical practice.

The exact time point when patients should be referred to intensive care may be difficult to identify and will likely depend on local clinical setup, *i.e.*, access to intermediate care. However, the following general consideration can be used. Dialogue between physicians from the referring ward and ICU is mandatory and should be initiated at an early stage to assess if the patient is candidate to intensive care if needed and to ensure detection and treatment of organ failures as early as possible.

Close monitoring of progressive organ dysfunction in

Intensive care candidate	Premorbid Child-Pugh A/B (5-9 points) or MELD score < 15 and ACLF grade ≤ 2 with the need for intensive therapy, <i>e.g.</i> , HE > 2 or respiratory insufficiency
Possible intensive care candidate, eligibility should be considered and discussed with ICU	Premorbid Child-Pugh A/B (5-9 points) or MELD score < 15 and ACLF grade ≥ 3 or Premorbid Child-Pugh C (10-15 points) or MELD score 16-29 and ACLF ≤ 2 If continuous organ failure is present after 3 d of complete intensive care treatment, the outcome is questionable
Unlikely to benefit from intensive care therapy Special cases can be discussed, <i>e.g.</i> , patients that are candidate for liver transplantation	Premorbid Child-Pugh C (10-15 points) or MELD score > 30 and ACLF grade ≥ 3

Figure 3 Proposal of a clinical system to identify candidates for intensive care if indicated. Algorithm based on three scoring systems: Child-Pugh Score, Model of End stage Liver Disease score (MELD) and Sequential Organ Failure Assessment score (CLIF-SOFA). ACLF: Acute on chronic liver failure; ICU: Intensive care unit.

the ward is essential. Sometimes it may also be rational to transfer patients to the intermediate care/ICU to prevent occurrence of organ failure by close monitoring. Referral criteria should include the following: (1) Comatose patients not able to protect airways; (2) Respiratory failure with need of mechanical ventilation; (3) Circulatory failure with systolic blood pressure < 90 mmHg or low mean arterial pressure (MAP < 60 mmHg) despite adequate fluid supplementation and increasing lactate or increasing creatinine or reduced urine output; (4) necessity of vasopressors; and (5) septic shock or multi-organ failures.

To help the daily registration of important values in patients with liver cirrhosis, we have developed a specific computer software program First Chronic Liver Allocation Scoring System (First-CLASS).

First-CLASS features an extensive data-gathering

First - CLASS

SSN: 112233-4455 Date: Sunday, March 01, 2015 12:00:00 AM

CHILD-PUGH SCORE

Bilirubin: 115 $\mu\text{mol/l}$

Albumin: 15 g/l

INR: 2.5

Ascites: Moderate / Seve

HE: Grade III

PREMORBIDE CHILD-PUGH SCORE

CP Score: 6 point

Date: 01/01/2015

MELD SCORE

Creatinine: 150 $\mu\text{mol/l}$

Dialysis: No

CLIF-SOFA SCORE

Sys / Dia: 105 / 60 mmHg

MAP: 75 mmHg

Vasopressor: None

Vasopressor volume: 0 $\mu\text{g/kg/min}$

O₂: 5 l/min

SAT: 93 %

PaO₂: kPa

SpO₂/FiO₂ or PaO₂/FiO₂: 200.59588 mmHg

EXTRA INFORMATION

Variceal haem. Yes

Septic shock: No

S. B. peritonitis: No

Alc. hepatitis: No

HRS: No

WHO perform: 2

Pulse: 92

Leukocytes: 10

RESULTS

Child-Pugh Score: 9

MELD Score: 29

CLIF-SOFA Score: 11

ACLF Grade: 2

Mortality:
28 days: 32.0%
90 days: 52.3%

Child-Pugh:
Class: B

CANDIDATE FOR INTENSIVE CARE UNIT

SAVE INFORMATION

SAVE

Figure 4 First Chronic Liver Allocation Scoring system. Danish civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth since 1968. HE: Hepatic encephalopathy; CP Score: Child Pugh Score; MAP: Mean arterial pressure; SAT: Oxygen saturation (%); Variceal Haemorrhage: Variceal haemorrhage; S.B. Peritonitis: Spontaneous bacterial peritonitis; Alco. Hepatitis: Alcoholic hepatitis; HRS: Hepato renal syndrome; WHO Perform: WHO performance status; ACLF grade: Acute on chronic liver failure grade; First-CLASS: First Chronic Liver Allocation Scoring System; SSN: Social Security Number.

tool, with a user-friendly graphical interface, for the purpose of scoring acute on CLIF patients. An immediate score of the patient is calculated using the described algorithm, and it will be presented to the user. All data is saved to a database, which can be easily retrieved for both research and evaluation of specific patients. First-CLASS provides a program for viewing the data that has been collected in a meaningful way, such as using graphs for visualization of results in the given admission period. Furthermore the First-CLASS-Viewer program allows for exporting the data of patients to be used directly for statistical analysis (Figure 4).

In conclusion, we found that the literature regarding allocation of cirrhotic patients to ICU is very limited and no studies have proposed and tested any specific allocation criteria. Thus it still remains to be determined, which cirrhotic patients will benefit from intensive care treatment, and if so, when during admission they should be transferred to the ICU, and when intensive treatment is futile and should be withheld. Based on indirect evidence we have proposed a scoring system that can help identify which patients are candidates or not to ICU therapy, however the system needs validation.

COMMENTS

Background

Patients with liver cirrhosis are prone to a progressive disease course with the occurrence of portal hypertension and hepatic failure leading to end-stage disease and development of complications. Cirrhosis and organ failure is associated with a high mortality. Rational and timely allocation to an intensive care unit (ICU) is a challenge of clinical importance.

Research frontiers

The exact time point when patients should be referred to intensive care may be difficult to identify and will likely depend on local clinical setup, *i.e.*, access to intermediate care. Close monitoring of progressive organ dysfunction in the ward is essential. Sometimes it may also be rational to transfer patients to the intermediate care/ICU to prevent occurrence of organ failure by close monitoring. Referral criteria should include the following: (1) Comatose patients not able to protect airways; (2) Respiratory failure with need of mechanical ventilation; (3) Circulatory failure with systolic blood pressure < 90 mmHg or low mean arterial pressure (MAP < 60 mmHg) despite adequate fluid supplementation and increasing lactate or increasing creatinine or reduced urine output; (4) necessity of vasopressors; and (5) septic shock or multi-organ failures.

Innovations and breakthroughs

To help the daily monitoring and registration of organfunctions in patients with liver cirrhosis, the authors have developed computer software program First Chronic Liver Allocation Scoring System (First-CLASS). First-CLASS features an extensive data-gathering tool, with a user-friendly graphical interface, for the purpose of scoring acute on chronic liver failure (CLIF) patients. An immediate

score of the patient is calculated using the described algorithm, and it will be presented to the user.

Applications

It still remains to be determined, which cirrhotic patients will benefit from intensive care treatment, and if so, when during admission they should be transferred to the ICU, and when intensive treatment is futile and should be withheld. Based on indirect evidence, the authors have proposed a scoring system that can help identify which patients are candidates or not to ICU therapy, however the system needs validation.

Terminology

Patients with cirrhosis presenting with acute hepatic deterioration and progressive organ failure represent the, now well described, syndrome Acute-on-Chronic-Liver Failure (ACLF). The CLIF ACLF in cirrhosis study investigators of the European Association for the Study of the Liver - Chronic Liver Failure Consortium originally introduced the concept of ACLF: "ACLF is based on the presence of three major characteristics of the syndrome; acute decompensation, organ failure (predefined by the CLIF SOFA score) and high 28-d mortality rate".

Peer-review

In this manuscript "Allocation of patients with liver cirrhosis and organ failure to intensive care: Systematic review and a proposal for clinical practice", the authors aimed to perform a systematic review regarding allocation of patients with liver cirrhosis to ICU. They also proposed a scoring system to help identify the patients as candidates for ICU therapy. The subject matter of current study is of interest. This review may help clinicians choose the more suitable treatments.

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